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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,612	03/29/2000	SERGIO ABRIGNANI	0366.103	7749

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EXAMINER	
WORTMAN, DONNA C	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/27/2002 17

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/509,612	ABRIGNANI ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 July 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *Please see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *7 and 27-31*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *PTO 892*

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit: 1648

With respect to Applicant's submissions of July 22, 2002, the computer readable copy and the paper copy of the sequence listing have been entered. Since the amendments to the specification at page 13 adding SEQ ID NO's that refer to Figure 1 and the amendments to the claims including SEQ ID NO's that were both part of the amendment after final under 37 CFR 1.116 have not been entered, however, the application remains not in compliance with the sequence rules to that extent. See 37 CFR 1.821(d).

The amendments to the specification and to the claims under 37 CFR 1.116 have not been entered since the proposed amendments to the claims would raise new issues under at least 35 USC 112, first and second paragraphs. Applicant's proposed amendment to claim 7 to change the preamble from "A method for treating an infection of HCV" to "A method for inhibiting binding of the E2 protein of HCV to human cells" would raise a new issue under 35 USC 112, second paragraph, for example, because it is not clear how much, or if, the scope of the claim is intended to be altered, since the original claim required treating an HCV infection by reducing the infectivity of the virus. Further, the proposed amended claim lacks language that clearly correlates the outcome of the claim with the preamble, since claim 7 as proposed to be amended recites "administering to a patient infected with HCV an amount of CD81 protein effective to bind HCV." These changes would also require additional consideration under 35 USC 112, first paragraph, as to whether the method as proposed to be recited is enabled.

If entered, the amendment to claim 7 to eliminate the recitation of "functional equivalent" would have overcome the rejection under 35 USC 112, second paragraph, based on the use of that terminology.

As Applicant has pointed out, the Pileri et al. reference (Hepatology 29:990-992, 1999) was referred to incorrectly in the previous Office action. Attached to this Advisory Action is a PTO 892 with the corrected citation.

With respect to the rejection of claims 7 and 27-31 under 35 USC 112, first paragraph, insofar as Applicant's arguments rely on proposed amendments to the claims as submitted in the after final amendment, the arguments are not persuasive since the amendments have not been entered; consequently, such limitations are not found in the claims. In addition, Applicant has argued (1) that it has been confirmed that CD81 binds to a properly folded HCV E1E2 heterodimer that retains native conformation and has submitted an Abstract of an article by Lambot et al. in support, which article is stated to be evidence that the CD81 EC2 loop binds HCV. Applicant has argued (2) that Petracca et al., of record, supports Applicant's position regarding therapeutic efficacy since Petracca et al. demonstrates that CD81 is a cellular receptor for HCV and binds HCV E2 with high affinity, and Applicant contends (3) that the present methods only require that HCV bind to the CD81 EC2 loop, which would leave less circulating virus and serve to decrease viral load. Applicant asserts (4) that using a CD81 protein that binds circulating HCV eliminates or reduces the amount of available virus for interacting with any cell surface receptor, including CD81. Applicant has submitted an Abstract of an article by Kishikawa et al. in support of the assertion (5) that

reducing viral load is desirable since HCV viral load is correlated with the likelihood of developing hepatocellular carcinoma. Applicant has stated (6) that "even if all HCV is not available to bind administered CD81, a beneficial result can still be obtained." Applicant has pointed out (7) that the possibility that the claims may read on inoperative embodiments is not a proper basis for a rejection under 35 USC 112, first paragraph, and has noted that Applicant is not required to establish "an unerring degree of effectiveness" of pharmaceutical compositions to be used as claimed.

Applicant's arguments have been considered but not found persuasive. With respect to points (1), (2), and (5), above, it is agreed, respectively, that CD81 EC2 binds to HCV E2 in its native conformation; that cellular CD81 binds to HCV; and that reducing HCV viral load would be desirable. With respect to point (3) and what the present claims require, it is again noted that since the amendment after final has not been entered, Applicant has made reference to limitations that are not in the claims; further, with or without the amendment, the claims are drawn to a pharmaceutical method since claim 7 recites "administering to a patient ...". Addressing point (4), there remains no factual evidence of record that administering to a patient a CD81 protein that binds circulating HCV would eliminate or reduce the amount of available virus for interacting with any cell surface receptor. Attorney's argument cannot substitute for evidence, and there is no evidence that concerns the *in vivo* fate of circulating HCV that is bound to soluble CD81. With respect to (6), Applicant's assertion that "even if all HCV is not available to bind administered CD81, a beneficial result can still be obtained" is speculation and, as pointed out above, is not supported by factual evidence of a

beneficial result. Addressing point (7), it is recognized that the possibility that the claims may read on inoperative embodiments is not a proper basis for a rejection under 35 USC 112, first paragraph, and it is recognized that Applicant is not required to establish "an unerring degree of effectiveness" of pharmaceutical compositions; however, the specification must enable one of skill to practice the invention throughout the scope of the claims, without undue experimentation, and with a reasonable expectation for success. Enablement for a method of using a protein as a pharmaceutical as claimed requires at least some factual basis for concluding that the *in vitro* results disclosed for CD81 protein can be extrapolated, with a reasonable expection for success, to an *in vivo* benefit to a human patient.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
August 26, 2002